

Comm.

CHRONIC PULMONARY DISEASES

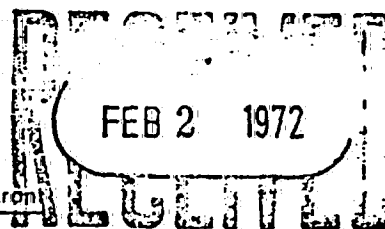
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#857 - 7/1/72 -
6/30/73

Dr. Gardner
Dr. Loosli
Dr. Wyatt

THE COUNCIL FOR TOBACCO RESEARCH - U.S.A., INC.

110 EAST 50TH STREET
NEW YORK, N. Y. 10022
(212) 421-8985



Application For Renewal of Research Grant
(Use extra pages as needed)

First Renewal ☒

Second Renewal ☐

Date: 1-31-73

1. Principal Investigator (give title and degrees):

Jerome I. Kleinerman, M. D.
Head, Division of Pathology Research & Clinical Pathology, St. Luke's Hospital
Professor of Pathology, Case Western Reserve University

2. Institution & address:

St. Luke's Hospital
11311 Shaker Blvd.
Cleveland, Ohio 44104

3. Department(s) where research will be done or collaboration provided:

Division of Pathology Research
Department of Pathology

4. Short title of study: Experimental Emphysema : The Effects of Prolonged Dust and Nitrogen Dioxide Exposure on the Physiologic and Morphometric Parameters of the Hamster Lung

5. Proposed renewal date: 7-1-73 -- 6-30-74

6. How results to date have changed earlier specific research aims:

No change

7. How results to date have changed earlier working hypothesis:

No change

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8. Any additional facilities now required? Describe briefly:

None

9. Any changes in personnel? Append biographical sketches of new key professional personnel:

Ronald Reschly, Research Assistant left because of entry into Medical School.

Replacement : Quantimet Technician, Joan Sorensen

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10. Append outline of experimental protocol for ensuing year. (Appended)

11. List publications or papers in press resulting from this or closely related work. (append reprints or manuscripts not previously sent). Niewoehner, D. E. and Kleinerman, J.: Effects of Experimental Emphysema and Bronchiolitis on Lung Mechanics and Morphometry. (Accepted for Publication) Journal Applied Physiology, 1973

Niewoehner, D. E. and Kleinerman, J.: Pulmonary Mechanics and Morphometry in Postmortem Human Lungs (submitted to American Thoracic Society, Jan. 1973)

Kleinerman, J. and Niewoehner, D. E.: Physiological, Pathological and Morphometric Studies of Long Term Nitrogen Dioxide Exposures and Recovery in Hamsters (submitted to American Thoracic Society, Jan. 1973)

12. Summary progress report (append in standard form as separate document, unless recently submitted).

13. Budget for the coming year:

A. Salaries (give names or state "to be recruited")

% time

Amount

Professional (give % time of investigator(s)
even if no salary requested)

Kleinerman, Jerome I. M. D.

20%

none

Technical

Harold, William, Physiology Technician
Townsend, Betty, Histologist
Sorensen, Joan, Quantimet Tech.
Cannon, Michael, Animal Caretaker25
50
25
153,974
5,842
3,500
1,098

Sub-Total for A

14,414

B. Consumable supplies (by major categories)

Animal Feed
Histology Supplies
Recording Paper for Physiological Studies

Sub-Total for B

2,000

C. Other expenses (itemize)

Sub-Total for C

None

Running Total of A + B + C

16,414

D. Permanent equipment (itemize)

Sub-Total for D

None

E

2,462

E. Indirect costs (15% of A+B+C)

18,876

Total request

10000

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14. Other sources of financial support:

List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Experimental Emphysema : Analysis of Mechanisms	NIH 2R01 ES00264-06A1 National Institutes of Health	40,000/yr	12-1-72 -- 11-30-77
A Correlative Study of Physi- ologic & Pathologic Findings in Obstructive Pul- monary Disease in Postmortem Lungs.	Nat'l Tuberculosis & Respiratory Disease Assoc.	10,587	7-1-72 -- 6-30-73
Evaluation of Heterozygous State for Human Alpha ₁ - Antitrypsin Deficiency	Ohio Thoracic Society	9,775	7-1-72 -- 6-30-73
Pulmonary Pathology in Cystic Fibrosis	Cystic Fibrosis Foundation	9,359	7-1-72 -- 6-30-73

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Relationship of Emphysema to Pulmonary Surfactant. An <u>In Vitro</u> and <u>In Vivo</u> Study	Ohio Thoracic Society	11,500	7-1-73 -- 6-30-74
A Correlative Study of Physi- ologic & Pathologic Findings in Obstructive Pul- monary Disease in Postmortem Human Lungs	Nat'l Tuberculosis & Respiratory Disease Assoc.	11,087	7-1-73 -- 6-30-74
Pulmonary Pathology in Cystic Fibrosis	Cystic Fibrosis Foundation	10,309	7-1-73 -- 6-30-74

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name Jerome Kleinerman, M. D.

Signature Jerome Kleinerman Date 1/31/73

Telephone 216 791-1000 Ext. 269
Area Code Number Extension

Checks payable to

Frank A. Oblak, Controller

Mailing address for check:

St. Luke's Hospital
11311 Shaker Blvd.
Cleveland, Ohio 44104

Responsible officer of institution

Typed Name Charles K. Arter, Jr.

Title President

Signature Charles K. Arter, Jr. Date 1/31/73

Telephone 216 791-1000 Ext. 424
Area Code Number Extension

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Procedure For The Ensuing Year

Exposures and the associated monitoring of NO₂ and dust concentrations will continue for at least 6-8 additional months.

An exact decision regarding the termination date will depend upon the health of the exposed animal colony, and local circumstances.

In any event exposures will probably not continue past 18 months.

At the time of sacrifice aliquots of animals from each of the experimental groups A) Dust only, B) Dust/NO₂ and Controls will be sacrificed at two periods following removal from exposure. One sacrifice period will be immediately following removal; a second

will occur from 2-4 weeks after removal. The latter sacrifice is to evaluate the reversibility of any functional or morphologic lesions which may be present. At the time of sacrifice the lungs

will be excised and measurement made following the protocol submitted in last years original application. In order not to be repetitious, the detailed protocol for this study will not be repeated. Studies will include static compliance, and dynamic compliance at 18, 45, 72 and 110 cycles per minute. Flow-volume curves during passive and forced deflation (the latter at -50 cm H₂O) will be performed, and expiratory flows, total pulmonary resistance, maximal expiratory flows and upstream resistances will be calculated. The mean values, standard deviations and standard error of the means will be calculated.

Analyses of any differences which may be found between means in the various groups will be compared by the student's "t" test and the probability of significance of these data determined.

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After physiologic studies, the lungs will be inflated at a constant pressure of 25 cm. H₂O and prepared for histologic study. This preparation will be carefully performed so that morphometric analyses can be done for calculation of mean linear intercept and internal surface area. In addition histologic study for abnormalities in the lung parenchyma, bronchi and bronchioles will be completed. Additional morphometric analyses will be done utilizing quantimet techniques for evaluation of goblet cell counts. For these studies tissues must be stained with the Alcian Blue-PAS technique. The extent, location and reaction about the pigment deposits in the lung will be studied to determine if the localization mimics that seen in human emphysema; if the pigment is intra or extracellular and if the cells ~~may~~ which contain pigment have invaded the interstitial tissue or merely exist within the alveolar spaces. The histologic study will be most valuable in determining whether exposure to the low NO₂ concentrations with dust can provoke the broncho-alveolar epithelialization so characteristic of higher levels of NO₂ exposure and if the epithelial papillary proliferation observed with higher doses of NO₂ also is provoked with the lower concentrations used in these studies. Finally the reversibility of the lesions which are seen immediately after sacrifice will be determined by study of hamsters sacrificed at the later period after removal from exposure.

The physiologic data including maximal expiratory flows, static recoil pressures and total pulmonary and upstream resistances will

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be compared between the various exposure groups to determine if exposure to a combination of dust and NO_2 causes greater functional abnormalities than dust alone. The relationship of L_m and ISA to elastic recoil pressure and maximal expiratory flows will be studied in all groups. The objectives of the correlations to be evaluated are to determine the effects of dust alone and in association with a low concentration of NO_2 on the physiologic and pathologic parameters of the lung.

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